PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44*bis*)

Applicant's or agent's file reference 002-ST-04-PCT	**FOR FURTHER ACTION**	See item 4 below
International application No. PCT/IT2005/000081	International filing date *(day/month/year)* 16 February 2005 (16.02.2005)	Priority date *(day/month/year)* 01 April 2004 (01.04.2004)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A.		

1. This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 *bis*.1(a).

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44*bis*.3(c) and 93*bis*.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44*bis* .2).

	Date of issuance of this report 04 October 2006 (04.10.2006)
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Simin Baharlou e-mail: pt09@wipo.int

Form PCT/IB/373 (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/IT2005/000081	International filing date *(day/month/year)* 16.02.2005
Priority date *(day/month/year)* 01.04.2004	
International Patent Classification (IPC) or both national classification and IPC A61K9/16, A61K47/34, A61K31/205, A61K9/70	
Applicant SIGMA-TAU INDUSTRIE FARMACEUTICHE RIUNITE S.P.A.	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IT2005/000081

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/IT2005/000081

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3,4,12,13,18
	No:	Claims	1,2,5-11,14-17,19
Inventive step (IS)	Yes:	Claims	3,4,12,13,18
	No:	Claims	1,2,5-11,14-17,19
Industrial applicability (IA)	Yes:	Claims	1-19
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present application relates to photocrosslinked PHEA-GMA-AA polymers, their compositions and their use as drug carriers, especially e.g. for acylcarnitine esters.

Reference is made to the following documents:

D1: PITARRESI G ET AL: BIOMATERIALS, vol. 25, no. 18, (2004), pages 4333-4343, disclosing photocrosslinked PHEA-GMA-AA polymers as in the present application, and their use as drug carriers;

D2: MANDRACCHIA DELIA ET AL: BIOMACROMOLECULES, vol. 5, no. 5, (2004), pages 1973-1982, cited in the application, disclosing the same photocrosslinked PHEA-GMA-AA polymers as in the present application and their use as drug carriers;

D3: US 4 071 508 A, disclosing anionic hydrogels constituted by three dimensional networks, comprising acid comonomers and photopolymerizable;

D4: US 6 458 386 B1 , disclosing crosslinked gelatin or dextran preparations for wound dressings;

D5: WO 00/45792 A, disclosing hydrogel particles for needleless injection;

D6: US 2003/152623 A1, disclosing pH-responsive "microgels" as drug carriers;

D7: GIAMMONA G ET AL: POLYMER, vol. 38, no. 13, (1997), pages 3315-3323, disclosing photocrosslinked polymers of PHEA - GMA;

D8: GIAMMONA G ET AL: BBA - GENERAL SUBJECTS, ELSEVIER SCIENCE PUBLISHERS, NL, vol. 1428, no. 1, (1999), pages 29-38, disclosing the same photocrosslinked polymers of PHEA - GMA; no further acid comonomers

The use of anionic crosslinked hydrogels for the production of matrices useful as drug carriers is well known in art (D3-D6, many others could be cited). The presence of acidic comonomers and the fact that the polymers can be crosslinked via irradiation with UV, gamma or other high energy radiation is also well known. According to the composition of the polymers, pH responsive behaviour can be obtained (e.g. D6);
therefore, the subject-matter of present claims 1,2,5-11,14-17,19 is not considered novel as required by the PCT Art. 33(1) and (2).

The particular polymers used in the present application in the examples are not described in any of the prepublished cited documents, as well as their use as carriers for acylcarnitine esters.
Similar polymers are used in D7 and D8. However, the latter documents fail to disclose the additional reaction with a further acidic comonomer like AA or MAA. The problem would be to improve the obtention process of the hydrogels. The solution proposed by the present application is to add AA or MAA to the known PHG. Apparently this allows to crosslink without the addition of initiators by simple irradiation. Thus, an inventive step could be acknowledged to present claims 3,4.

PH-dependent release hydrogel matrix preparations fo acylcarnitines with good release properties in the intestinal tract are not disclosed nor suggested in the cited prior art. Claims 12, 13 and 18 could be considered inventive as well.

Re Item VI

Certain documents cited

The potentially relevant intermediate documents D1 and D2 are quoted according to Rules 70.10 and 64.3 PCT.

Re Item VIII

Certain observations on the international application

The expression "suitably" in claim 1 is considered unclear (Art. 6 PCT).